Targeting Cholesterol Metabolism in Macrophages to Eliminate Viral Infection

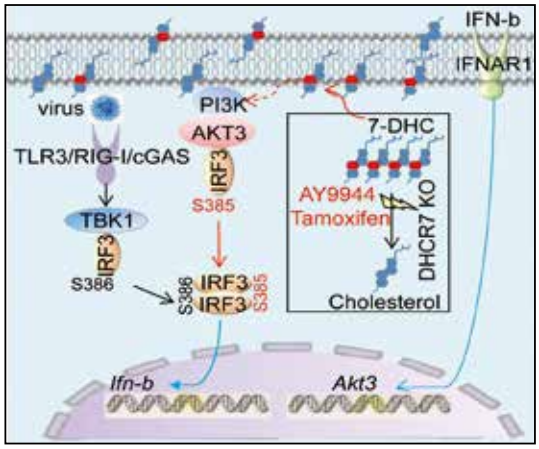
Recent evidence suggests a link between cholesterol metabolism and innate immunity. Upon viral infection, macrophages show reduced cholesterol synthesis, which is accompanied by enhanced expression of antiviral genes including type I interferon (IFN-I). IFN-I can induce 25-hydroxycholesterol (25-HC) accumulation, and 25-HC blocks viral entry. However, it remains unclear whether other cholesterol metabolic products or enzymes are connected with innate immunity, until a recent research conducted by a joint team of biologists in Shanghai shed new light on this.

In their research, WANG Hongyan's team from the Center for Excellence in Molecular and Cellular Science (Institute of Biochemistry and Cell Biology, SIBCB), Chinese Academy of Sciences (CAS) explored the possible regulative role of enzyme DHCR7 and a natural cholesterol metabolite 7DHC in immune responses. In collaboration with Prof. WEI Bin at Shanghai University, a former PI of the Wuhan Institute of Virology of CAS, the researchers screened the expression levels of multiple enzymes that regulate cholesterol metabolism to identify the differentially expressed enzymes in the liver tissue from HCC patients with hepatitis B virus infection, and also that from mice or macrophages infected with vesicular stomatitis virus (VSV).

The expression level of DHCR7 (7-dehydrocholesterol reductase) is significantly reduced in livers and macrophages upon viral infection. DHCR7 is an enzyme that converts 7-dehydrocholesterol (7-DHC) into cholesterol. Patients carrying Dhcr7 mutations show development defects and mental retardation. However, the role of DHCR7 in innate immunity is unclear. The study shows that DHCR7 knock-out (KO) macrophages or the DHCR7 inhibitor treated macrophage could promote IRF3 activation and enhance type I interferon (IFNβ) production to clear multiple viruses *in vitro* or *in vivo*.

Interestingly, the team's research revealed that Tamoxifen, a chemotherapy drug used to treat breast cancer approved as an inhibitor to reduce DHCR7's enzyme activity by the U.S. Food and Drug Administration, can also inhibit infection by VSV and the Zika virus at the cellular level, suggesting a possible application for Tamoxifen as an anti-viral infection drug.

In addition, they found that mice treated with the DHCR7 inhibitor AY9944 showed a significant increase in serum 7-DHC concentration, which promoted IRF3 phosphorylation and enhanced IFNβ production in macrophages, thus protecting mice against lethal doses of VSV or the H1N1 influenza virus.



A recent work by the team led by Dr. WANG Hongyan at SIBCB have elucidated that the enzyme DHCR7 and the natural cholesterol metabolite 7DHC can regulate viral infection. This study was published online in *Immunity* on Dec 25th 2019.

Mechanistically, the research revealed that viral infection can enhance AKT3 expression, and 7-DHC treatment could activate AKT3. AKT3 directly binds and phosphorylates IRF3 at Ser385, together with TBK1-induced phosphorylation of IRF3 Ser386, to achieve full activation of IRF3.

In conclusion, this study demonstrates that both the cholesterol metabolite 7-DHC and the DHCR7 inhibitors promote IFN-I production and increase antiviral responses by activating AKT3 and IRF3. This research provides new insights into how cholesterol metabolism regulates innate immunity, which also helps to develop new drugs against anti-viral infections.

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Reference: https://www.sciencedirect.com/science/article/pii/S1074761319304960?via%3Dihub

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